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REVIEW

Extracellular vesicles in metabolic dysfunction-associated steatotic liver disease: From intercellular signaling to clinical translation

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) poses a substantial global health burden, progressing from simple steatosis to metabolic dysfunction-associated steatohepatitis and cirrhosis. A deeper understanding of the underlying mechanisms and associated complications is crucial for developing effective therapies. Extracellular vesicles (EVs), nanoscale membrane-enclosed particles carrying bioactive cargoes such as proteins and noncoding RNAs, including microRNAs and long noncoding RNAs, play crucial roles in intercellular communication and have emerged as critical mediators of MASLD pathogenesis. This article details the current understanding of the function of EVs in MASLD progression, emphasizing specific cell-derived EVs implicated in disease development. We elucidate how EVs facilitate intercellular communication and influence key pathological processes, including lipotoxicity, inflammation, and fibrosis. Furthermore, we examine the involvement of EVs in MASLD-associated complications and evaluate their potential as minimally invasive tools for disease diagnosis, staging, and prognosis. We also explore EV-based therapeutic strategies, encompassing preclinical studies, while acknowledging current challenges and future opportunities. Finally, we discuss emerging research trends, the potential for personalized medicine, and areas necessitating further investigation, particularly the utilization of EVs as therapeutic targets or delivery vehicles. This review underscores the pivotal role of EVs in MASLD, providing insights into their translational potential for improved patient outcomes.

Key Words: Metabolic dysfunction-associated steatotic liver disease; Metabolic

dysfunction-associated steatohepatitis; Extracellular vesicles; Fibrosis; Lipotoxicity

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Core Tip: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing global health concern that progresses from simple steatosis to cirrhosis. Extracellular vesicles (EVs) have emerged as key mediators of MASLD pathogenesis, influencing lipotoxicity, inflammation, and fibrosis through bioactive cargoes such as microRNAs. This review highlights the role of EVs in MASLD progression, their diagnostic and prognostic potential, and EV-based therapeutic strategies. We also address current challenges, emerging research trends, and future perspectives, emphasizing the translational potential of EVs for improving patient outcomes.

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INTRODUCTION

The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), the updated nomenclature for steatotic liver disease associated with metabolic syndrome, has rapidly increased, becoming a leading global health challenge. It affects approximately 30% of the worldwide population and represents the most prevalent form of chronic liver disease[1-4]. Indeed, the global prevalence of MASLD is expected to rise in the coming decade, mirroring the growing worldwide epidemics of obesity and type 2 diabetes[5,6]. A 2022 systematic review reported a global MASLD prevalence of 32.4%, a substantial increase from the 25.5% reported between 1990 and 2022[7]. While cardiovascular disease (CVD) remains the primary cause of mortality in patients with MASLD, those with advanced liver fibrosis face a dramatically increased risk of liver-related death[8,9]. The incidence of MASLD closely parallels the increasing prevalence of obesity and type 2 diabetes, underscoring its strong association with metabolic syndrome. The role of environmental modifiers such as diet, lifestyle, and the gut microbiota further contributes to the increasing prevalence of metabolic syndrome components, including obesity, diabetes, and hypertension, which in turn drive MASLD incidence[10,11].

MASLD encompasses a spectrum of chronic liver disorders, beginning with simple hepatic steatosis, characterized by excessive triglyceride accumulation in hepatocytes[12,13]. This condition can progress to more severe metabolic dysfunction-associated steatohepatitis (MASH), which is characterized by inflammation and hepatocyte injury. Untreated MASH can lead to fibrosis, cirrhosis, and ultimately, hepatocellular carcinoma (HCC)[14,15]. While the disease affects a large portion of the population and poses a significant risk of liver-related mortality, especially in advanced stages, there is a lack of approved drug therapies. This critical gap underscores the urgent need for innovative therapeutic and diagnostic strategies[16].

Central to the pathogenesis of MASLD is the complex interplay of intercellular communication, where extracellular vesicles (EVs) are increasingly recognized as pivotal mediators. EVs are lipid bilayer-enclosed, nonreplicative particles released by all cells into the extracellular space and circulation. EVs are classified on the basis of size: Large EVs (100-1000 nm, primarily < 400 nm) are associated with microvesicle markers, whereas small EVs (40-200 nm) are characterized by exosome markers. The two major classes of EVs - exosomes and microvesicles - differ in their biogenesis and functional roles. Microvesicles range from 70 nm to nearly 1 μm in size and bud directly from the plasma membrane, whereas exosomes originate within the endosomal system before secretion and typically range from 50 nm to 150 nm in size[17,18]. These vesicles serve as crucial vehicles for intercellular communication, and transport of cargo of proteins, DNA, and RNA, including mRNAs, microRNAs (miRNAs), and long noncoding RNAs (lncRNAs), thereby modulating molecular pathways in recipient cells[19]. The composition of EVs reflects the physiological or pathological state of their originating cells, making them dynamic indicators of disease progression[20-22]. In MASLD, hepatocyte-derived EVs, particularly in response to lipotoxicity, contribute significantly to the inflammatory milieu by influencing macrophage activity, thus playing a critical role in disease pathogenesis[23,24].

This review aims to provide a comprehensive overview of the role of EVs in MASLD, bridging the gap between basic mechanistic insights and potential clinical applications. Specifically, we explore the fundamental biology of EVs, delineate their involvement in MASLD pathogenesis, and critically assess their potential as diagnostic biomarkers, therapeutic delivery vehicles, and targets for therapeutic intervention. We also address the inherent challenges associated with EV research and clinical translation, providing a holistic perspective on the current state of knowledge in this rapidly evolving field.

EV AND MASLD PATHOGENESIS

Mechanisms of EV release and uptake in the liver

Biogenesis and secretion by liver cells: The biogenesis and secretion of EVs are complex processes, and their precise regulation remains incompletely understood. As mentioned above, research on EVs has focused widely on exosomes and microvesicles. While exosomes and microvesicles arise through distinct biogenetic pathways, they share fundamental regulatory mechanisms for their formation and release[25]. Exosomes originate from the endosomal pathway, where inward budding of endosomal membranes results in the formation of intraluminal vesicles within multivesicular bodies (MVBs)[26,27]. These MVBs either fuse with the plasma membrane to release exosomes or are directed to other cellular compartments. Exosome biogenesis can be categorized into endosomal sorting complex required for transport (ESCRT)-dependent and ESCRT-independent pathways. The ESCRT complex, comprising several protein subunits, is crucial for cargo sorting and intraluminal vesicle formation, facilitating the selection, clustering, and membrane scission of cargo proteins[28,29]. However, even in the absence of ESCRT components, exosomes can still form, with lipids such as bismonoacylglycerophosphate and phosphatidic acid playing alternative roles[30,31]. Ceramides also contribute to ESCRT-independent exosome formation, influencing cargo selection through sphingosine 1-phosphate (S1P) signaling [32]. Cargo sorting into exosomes is a selective process, with tetraspanins and various signaling pathways determining the inclusion of specific proteins and RNAs. Rab GTPases regulate MVB trafficking, docking, and fusion with the plasma membrane, impacting exosome secretion in a cell type-specific manner[33]. By contrast, microvesicles form through outward budding of the plasma membrane and are influenced by protein aggregation, lipid composition, and cytoskeletal rearrangements. Like exosomes, ESCRT proteins and ceramides participate in microvesicle formation, although the lipid and protein contents of microvesicles are highly heterogeneous[34].

The release of EVs is an energy-dependent process that is intricately regulated by cellular stress, nutrient availability, and signaling pathways, thereby modulating EV secretion across diverse cell types[35]. Although directly detecting EV production *in vivo* remains a technological hurdle, *in vitro* studies have demonstrated that numerous liver cell types, including hepatocytes, hepatic stellate cells (HSCs), liver sinusoidal endothelial cells (LSECs), and Kupffer cells, are capable of EV production. In particular, hepatocytes release EVs, the production of which exhibits both qualitative and quantitative variations in response to cellular stimuli and disease states. Specifically, stressors such as lipotoxic endoplasmic reticulum stress and hypoxia induce significant changes, indicating a strong correlation between EV release and hepatic pathology[36].

Mechanisms of EV uptake by recipient cells: Once released, they initiate cellular responses to induce functional changes in recipient cells by transporting bioactive molecules such as proteins and RNAs to distant targets. This delivery necessitates the internalization of EVs through two primary mechanisms: Direct membrane fusion or endocytic internalization[37,38]. Direct membrane fusion involves the integration of the EV lipid bilayer with the recipient cell plasma membrane, whereas endocytosis involves the engulfment of EVs by the target cell[39]. Several proposed endocytosis pathways include clathrin-mediated endocytosis, caveolin-dependent endocytosis, macropinocytosis, phagocytosis, and lipid raft-mediated internalization[40-42]. The precise mechanisms governing endocytosis remain a subject of ongoing investigation; however, evidence suggests that EV uptake can be cell type-specific[43]. The specific mechanisms of EV uptake can vary among recipient cell types. Studies using fluorescently labeled EVs have demonstrated that recipient cells primarily internalize EVs through controlled endocytosis. For example, neurons predominantly utilize clathrin-mediated endocytosis, epithelial cells may utilize caveolin-dependent endocytosis, and tumor cells may rely on lipid raft-dependent endocytosis[44-46]. Additionally, specific protein-protein interactions play crucial roles in EV uptake. EVs typically attach to recipient cells and are internalized through interactions involving membrane receptors, ligands, or contact proteins. Proteins such as tetraspanins, lectins, and integrins, along with glycosylation processes, facilitate these interactions and influence EV uptake[47-51]. Notably, EVs may utilize multiple routes of internalization, depending on the surface proteins present on both the vesicle and the target cell[38].

In the liver, these cells are internalized by various cell types, contributing to critical physiological processes such as macrophage modulation and HSC activation (Figure 1). Previous studies have shown that liver macrophages can take up melanoma cell line-derived EVs labeled with PKH26 fluorescent dye following intravenous administration[52]. Notably, EVs loaded with miRNA-155 (miR-155) showed rapid distribution and uptake in the liver, with the majority of miR-155 found in both hepatocytes and liver mononuclear cells within minutes of injection. This quick uptake and clearance of EVs from the circulation highlights the significant role of the liver in EV processing[53]. Moreover, EVs released from hepatocytes transfer components necessary for S1P synthesis to recipient hepatocytes, thereby promoting cell growth and liver repair following ischemia/reperfusion injury or partial hepatectomy[54]. While these studies collectively highlight the capacity of EV cargo to elicit biological responses in recipient liver cells, the precise mechanisms governing EV internalization by these cells remain incompletely understood. A recent study revealed that in MASLD, lipotoxic hepatocytes induced by palmitic acid (PA) selectively take up apolipoprotein E (ApoE)-containing EVs from neutrophils, facilitating miR-223 transfer through a low-density lipoprotein receptor (LDLR)-dependent mechanism[55]. This LDLR/ApoE pathway is also involved in the uptake of macrophage-derived miR-223-enriched EVs by lipotoxic hepatocytes. However, the impact of lipotoxicity on hepatocyte LDLR expression remains unclear, with studies reporting both increased and decreased LDLR levels[56]. Furthermore, molecules such as statins, which are known to influence LDLR expression and cholesterol uptake, may also play a role in EV uptake in the liver. While statins have been shown to increase LDLR expression and low-density lipoprotein-derived cholesterol uptake in HepG2 hepatoma cells, further research is needed to determine whether they similarly increase EV uptake in hepatocytes[57,58]. In summary, while evidence suggests that liver cells internalize EVs through various mechanisms, further investigation is needed to fully elucidate the specific pathways involved.

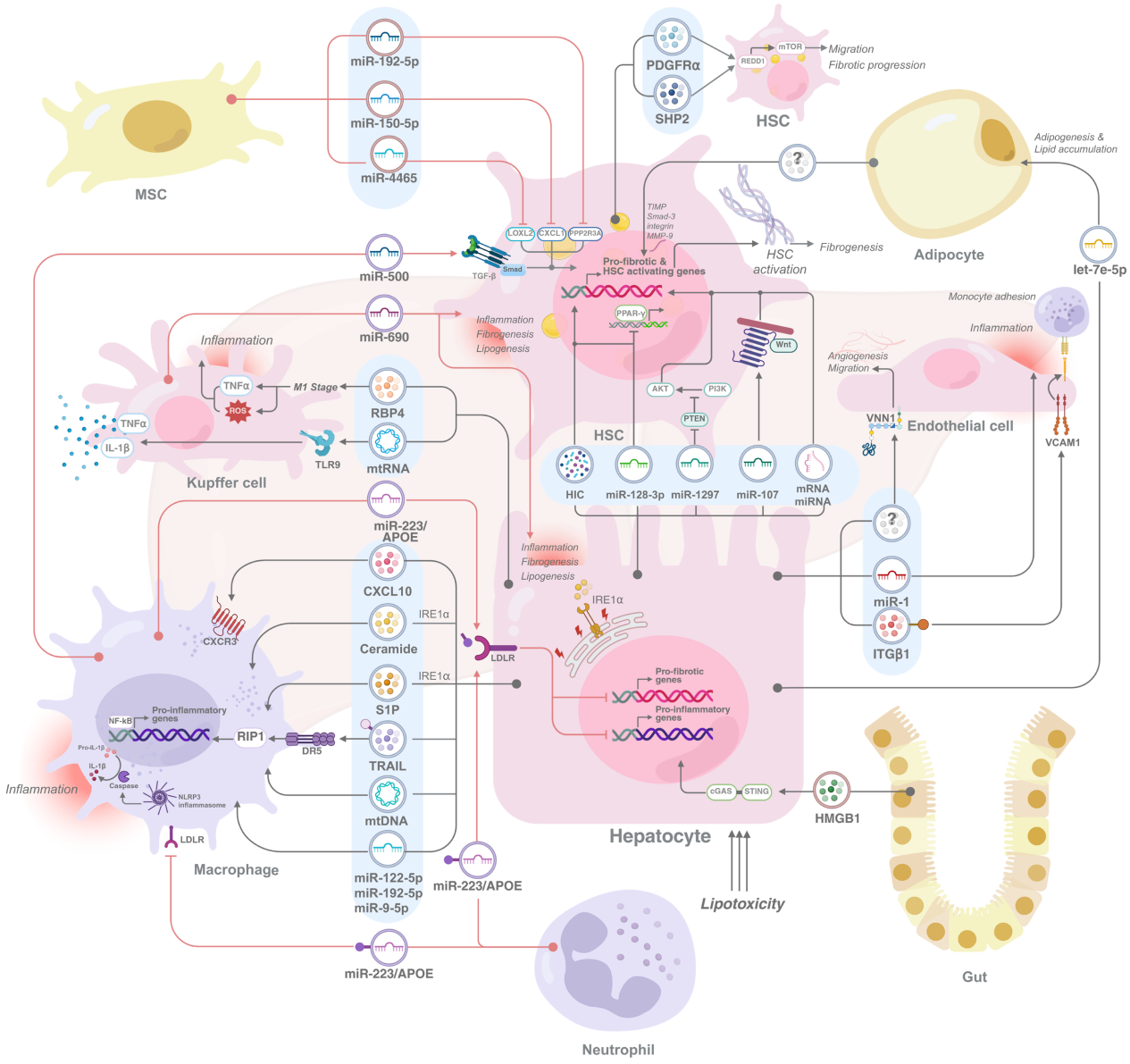

Figure 1 Extracellular vesicle-mediated cellular interactions in metabolic dysfunction-associated steatotic liver disease pathogenesis. Extracellular vesicles (EVs), which act as key mediators of intercellular communication, facilitate the transfer of bioactive molecules, including proteins, lipids, and microRNAs, thereby significantly influencing recipient cell phenotypes and driving pathological processes. These EVs, which originate from diverse sources, such as hepatocytes, immune cells, and hepatic stellate cells (HSCs), contribute to the complex interplay of inflammation, fibrosis, lipid accumulation, and angiogenesis that characterizes metabolic dysfunction-associated steatotic liver disease (MASLD). Specifically, hepatocyte-derived EVs have been shown to activate macrophages, HSCs, endothelial cells, and adipocytes, thus promoting disease progression. Furthermore, immune cell-derived EVs play dual roles and are capable of both exacerbating and ameliorating MASLD. EVs from adipose tissue enhance fibrogenesis, whereas those from mesenchymal stem cells suppress HSC activation, highlighting their potential therapeutic implications. Finally, gut-derived EVs are implicated in further aggravating liver pathology in MASLD, underscoring the systemic impact of EV-mediated communication in this disease. mtDNA: Mitochondrial DNA; MSC: Mesenchymal stem cell; TNF-α: Tumor necrosis factor alpha; IL: Interleukin; RBP4: Retinol binding protein 4; APOE: Apolipoprotein E; TLRs: Toll‐like receptors; NF-κB: Nuclear factor kappa B; CXCL: C-X-C motif chemokine ligand; CXCR: C-X-C motif chemokine receptor; R1P1: Receptor interacting protein kinase 1; miR: MicroRNA; HSC: Hepatic stellate cell; PDGFRα: Platelet derived growth factor receptor alpha; SHP2: Src homology region 2 domain‐containing phosphatase 2; VNN1: Vanin 1; ITGβ1: Integrin beta 1; HMGB1: High mobility group box 1; VCAM1: Vascular cell adhesion molecule 1.

EV-mediated intercellular communication in MASLD

EVs play a crucial role in intercellular communication by transferring bioactive cargo from donor cells to recipient cells, thereby influencing various pathological processes in MASLD. Previous studies have demonstrated that elevated levels of circulating EVs in both patients and animal models correlate with liver injury, inflammation, and fibrosis, highlighting their importance in disease progression. EVs released from hepatocytes, immune cells, and HSCs carry diverse molecular cargo, including proteins, lipids, and nucleic acids, which alter the phenotype and function of recipient cells[59-62]. For example, the transfer of EVs from high-fat diet (HFD)-fed mice to healthy mice induces liver inflammation and damage by activating and directing immature myeloid cells to the liver, resulting in elevated levels of proinflammatory molecules and liver enzymes[63]. These findings underscore the role of EVs as mediators of intercellular communication in MASLD pathogenesis. The following sections discuss the involvement of EVs in different cell types, as summarized in Table 1 and

Table 1 Extracellular vesicle cargo and functional effects in metabolic dysfunction-associated steatotic liver disease progression

Donor cells/ EV sources	Recipient cells	EV cargoes	EV effects	Ref.
Hepatocyte-derived EVs to other cells				
Lipotoxic hepatocytes, primary mouse hepatocytes and Huh7 cells treated with PA or LPC	Macrophages, BMDMs	CXCL10	Recruits macrophages and exacerbates inflammation	[65,67]
Lipotoxic hepatocytes, mouse hepatocyte cell lines, primary mouse hepatocytes, and Huh7 cells treated with PA or OA	Macrophages, BMDMs	Ceramide, S1P	Activates IRE1α, recruits macrophages, and amplifies liver inflammation	[36,68]
Lipotoxic hepatocytes, primary mouse hepatocytes and Huh7 cells treated with LPC	Macrophages, BMDMs	TRAIL	Activates macrophages *via* RIP1-DR5 pathway, worsening inflammation	[64]
Primary mouse hepatocytes	Macrophages, RAW264.7 cells	mtDNA	Activates macrophages, increasing inflammatory signaling	[24]
Lipotoxic hepatocytes, LO2 cells treated with PA, Huh7 cells treated with ox-LDL and MβCD cholesterol	Macrophages, THP-1 cell diferentiation	miR-122-5p, miR-192-5p, miR-9-5p	Polarizes macrophages to M1, enhances inflammatory responses	[70,71,72]
Hypoxia in fat-laden liver cells, primary mouse hepatocytes and HepG2 treated with PA + OA	HFD-mouse Kupffer cells	mtDNA	Activates TLR9, inducing TNFα and IL-1β secretion	[73]
Primary rat hepatocytes	Primary rat Kupffer cells	N/A	Stimulates inflammation in Kupffer cells	[74]
Lipotoxic hepatocytes, LO2 cells treated with PA	Primary human Kupffer cells	RBP4	Promotes M1 polarization, increases ROS and TNF-α production	[75]
Lipotoxic hepatocytes, HepG2 treated with PA + OA, chemical hypoxia induction hepatocytes, treated with $CoCl_2$	HSCs, LX-2 cells	Hypoxia-induced cargo	Promotes pro-fibrotic gene expression and fibrosis	[66,76]
Lipotoxic hepatocytes, primary mouse hepatocytes and HepG2 cells treated with PA	HSCs, LX-2 cells, primary mouse HSCs	miR-128-3p	Suppresses PPAR-γ, enhances pro-fibrogenic gene expression, proliferation, and chemotactic responses	[66]
Lipotoxic hepatocytes, primary hepatocytes, LO2 cells treated with PA	HSCs, LX-2 cells	miR-1297	Targets PTEN, leading to HSC activation and proliferation *via* PI3K/AKT signaling	[77]
Lipotoxic hepatocytes, primary hepatocytes treated with PA	HSCs, LX-2 cells	miR-107	Activates Wnt signaling, promoting HSC activation	[78]
Lipotoxic hepatocytes, primary rat hepatocytes treated with PA + OA	HSCs, primary rat HSCs	Various mRNAs and miRNAs	Induces pro-fibrotic and pro-senescent phenotype, reduce fibrosis, increase ROS and senescence markers, mediated *via* AKT-mTOR pathway	[79]
Lipotoxic hepatocytes, primary rat hepatocytes, HepG2 cells treated with PA	Endothelial cells, primary rat endothelial cells, HUVECs	VNN1	Promotes angiogenesis and endothelial migration	[61]
Lipotoxic hepatocytes, primary mouse hepatocytes, Huh7 cells treated with PA	Endothelial cells, primary rat endothelial cells, HUVECs	miR-1	Promotes endothelial inflammation and atherogenesis	[80]
Lipotoxic hepatocytes, primary mouse hepatocytes, Huh7 cells treated with LPC	Endothelial cells, primary mouse LSECs	ITGβ1	Induces monocyte adhesion to LSECs, facilitating inflammation and fibrosis	[81]
Primary mouse hepatocytes	Adipocytes, 3T3-L1 cell differentiation	let-7e-5p	Promotes adipogenesis and lipid accumulation	[82]
Immune cell-derived EVs to other cells				
Neutrophills isolated from CCL4- and MCD-treated mice	Macrophages, mouse primary hepatic macrophages	miR-223	Promotes restorative macrophage phenotype, reduces HSC activation and fibrosis	[84]
Neutrophills isolated from HFD-	Lipotoxic hepatocytes, AML12	miR-223	Inhibits hepatic inflammatory and	[55]

treated mice	cells treated with PA		fibrogenic gene expression in LDLR/ApoE dependent manner	
Macrophages and neutrophils isolated from IL-6 knockout HFD-treated mice	Hepatocytes, primary mouse hepatocytes	miR-223	Suppresses fibrotic gene and immflmatory gene expression, reducing liver fibrosis	[87]
Macrophages, human PBMC dirferentiation	Lipotoxic hepatocytes, Huh7 treated with PA	miR-223	Reduces inflammatory and fibrotic responses within the liver by suppressing FOXO3 and TAZ through LDLR/ApoE axis	[56]
Macrophages, RAW264.7 cells	HSCs, primary mouse HSCs isolated from CCL4-induced mice	miR-500	Activates TGF-β/Smad pathway, accelerating fibrosis	[88]
Kupffer cells isolated from MASH mice	Hepatocytes, HSCs isolated from MASH mice	miR-690	Regulates inflammation, fibrogenesis, and lipogenesis	[89]
Other cell-derived EVs				
Visceral adipose tissue isolated from obese and lean patients	HSCs	N/A	Alters liver matrix regulation by increasing TIMP, Smad-3, integrin, and MMP-9 expression in HSCs	[90]
HSCs, primary human HSCs, LX-2 cells	HSCs, primary human HSCs, LX-2 cells	PDGFRα, SHP2	Promotes HSC migration and fibrosis progression by suppressing REDD1 and enhancing mTOR	[91,92]
BMSCs	HSCs	miR-192-5p	Inhibits HSC activation by targeting PPP2R3A	[93]
ADMSCs isolated from CCl4-induced mice	HSCs	miR-150-5p	Suppresses CXCL1, reducing fibrosis	[94]
MSCs isolated from the human umbilical cords	HSCs, LX-2 cells	miR-4465	Reduces fibrosis by altering LOXL2 expression	[95]
Gut-derived EVs, HFD-fed mice	Hepatocytes, HSCs, HFD-fed mice, Mki67 mice	HMGB1	Activates cGAS/STING pathway, driving inflammation and fibrosis	[96,97]

EV: Extracellular vesicle; MASLD: Metabolic dysfunction-associated steatotic liver disease; MASH: Metabolic dysfunction-associated steatohepatitis; PA: Palmitic acid; LPC: Lysophosphatidylcholine; BMDMs: Bone marrow-derived macrophages; CXCL: C-X-C motif chemokine ligand; OA: Oleic acid; S1P: Sphingosine-1-phosphate; IRE1α: Inositol-requiring enzyme 1 alpha; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand; RIP1-DR5: Receptor-interacting serine/threonine-protein kinase 1-death receptor 5; mtDNA: Mitochondrial DNA; ox-LDL: Oxidized low-density lipoprotein; MβCD: Methyl-β-cyclodextrin; HFD: High-fat diet; TLR9: Toll-like receptor 9; TNFα: Tumor necrosis factor alpha; IL-1β: Interleukin-1 beta; LO2: Human normal liver cell line LO2; RBP4: Retinol-binding protein 4; ROS: Reactive oxygen species; HSCs: Hepatic stellate cells; PPAR-γ: Peroxisome proliferator-activated receptor gamma; PTEN: Phosphatase and tensin homolog; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; AKT-mTOR: Protein kinase B-mammalian target of rapamycin; VNN1: Vanin 1; HUVECs: Human umbilical vein endothelial cells; ITGβ1: Integrin subunit beta 1; LSECs: Liver sinusoidal endothelial cells; CCL4: Carbon tetrachloride; MCD: Methionine-choline deficient; LDLR: Low-density lipoprotein receptor; ApoE: Apolipoprotein E; TGF-β: Transforming growth factor beta; Smad: Small mothers against decapentaplegic; TIMP: Tissue inhibitor of metalloproteinases; MMP-9: Matrix metalloproteinase 9; PDGFRα: Platelet-derived growth factor receptor alpha; SHP2: Src homology region 2 domain-containing phosphatase-2; REDD1: Regulated in development and DNA damage responses 1; mTOR: Mammalian target of rapamycin; BMSCs: Bone marrow mesenchymal stem cells; PPP2R3A: Protein phosphatase 2 regulatory subunit B alpha; ADMSCs: Adipose-derived mesenchymal stem cells; CXCL1: C-X-C motif chemokine ligand 1; MSCs: Mesenchymal stem cells; HMGB1: High mobility group box 1; cGAS/STING: Cyclic guanosine monophosphate–adenosine monophosphate synthase/stimulator of interferon genes; N/A: Not applicable; FOXO3: Forkhead box O3; TAZ: Transcriptional coactivator with PDZ-binding motif.

Figure 1.

Hepatocyte-derived EVs: Hepatocytes, the primary cells affected by lipotoxicity, are the most extensively studied source of EVs in MASLD. Given the complexity of MASLD pathology, EV-mediated crosstalk has gained significant attention, particularly with a focus on EVs released from hepatocytes. Researchers have modeled lipotoxicity by inducing lipid accumulation in hepatocytes *via* saturated free fatty acids (FFAs), such as PA (C16:0), oleic acid (C18:1), or lysophosphatidylcholine[64]. Notably, PA not only stimulates lipid storage but also promotes EV release from hepatocytes[65,66]. Upon lipotoxicity induction, mixed linage kinase activation triggers the mitogen-activated protein kinase signaling cascade, leading to signal transducer and activator of transcription 1 phosphorylation and enhanced C-X-C motif chemokine ligand (CXCL) 10 transcription. The subsequently released CXCL10-bearing EVs are internalized into macrophages by binding to C-X-C motif chemokine receptor 3, thereby driving inflammation[65,67]. Similarly, hepatocyte-derived EVs enriched with ceramide activate inositol-requiring enzyme 1 alpha and promote S1P production, further recruiting macrophages to amplify liver inflammation. Additionally, elevated plasma EV ceramide levels have been observed in patients with MASH, underscoring their role in disease progression[36]. S1P-rich EVs act as a signal, attracting macrophages *via* the S1P1 receptor, leading to their persistent movement toward liver tissue. This signaling pathway contributes to macrophage infiltration during liver damage in MASH[68]. Lipotoxic hepatocytes also exacerbate

inflammation by releasing tumor necrosis factor-related apoptosis-inducing ligand-bearing EVs that trigger macrophage activation *via* a receptor-interacting protein kinase 1-dependent, noncanonical death receptor 5 pathway[24]. Moreover, exogenous overexpression of CXCL1 in hepatocytes promotes hepatic neutrophil infiltration and reactive oxygen species (ROS) production. ROS-damaged hepatocytes release EVs carrying mitochondrial DNA (mtDNA), which also activates macrophages, underscoring the diverse inflammatory signals mediated by EV cargo. The administration of interleukin (IL)-22 has been shown to suppress this inflammatory response, suggesting a potential therapeutic approach to reduce mtDNA-induced signaling in MASH[69]. This progression highlights the intricate pathways through which EVs facilitate macrophage recruitment and activation, exacerbating liver inflammation.

In addition to direct inflammatory signaling, lipotoxic hepatocytes release EVs carrying specific miRNAs, which influence the phenotype of recipient cells. For example, cholesterol-exposed hepatocytes release EVs containing miR-122-5p, which polarizes macrophages into the proinflammatory M1 subtype[70]. EVs carrying miR-192-5p activate macrophages and increase the expression of inflammatory molecules, including inducible nitric oxide synthase, IL-6, and tumor necrosis factor alpha (TNF-α), through the modulation of Rictor, a key component of the rapamycin-insensitive mammalian target of rapamycin (mTOR) complex, which inhibits the phosphorylation of the protein kinase B (AKT) and forkhead box O1 (Rictor/AKT/forkhead box O1) signaling pathways[71]. Additionally, miR-9-5p in hepatocyte-derived EVs suppresses transglutaminase 2 expression, promoting macrophage polarization and exacerbating inflammation[72]. This miRNA-mediated communication illustrates the sophisticated control hepatocytes exert over immune responses in MASLD, extending beyond chemokine signaling.

EVs facilitate communication between lipotoxic hepatocytes and Kupffer cells, the resident macrophages of the liver, perpetuating liver inflammation. Hepatocyte-derived EVs containing mtDNA act as danger signals, activating Toll-like receptor 9 on Kupffer cells and triggering the release of TNFα and IL-1β, thereby driving liver damage[73]. EVs released from hypoxic, lipid-laden hepatocytes stimulate inflammation in Kupffer cells, as determined by the increased levels of proinflammatory cytokines and inflammasome components, including IL-1β, NOD-like receptor pyrin domain containing 3 (NLRP3), and apoptosis-associated speck-like protein containing[74]. Hepatocytes release EVs carrying retinol-binding protein 4, which triggers M1-like polarization in Kupffer cells. This activation, which is mediated by nicotinamide adenine dinucleotide phosphate oxidase 2 and nuclear factor kappa B (NF-κB), leads to increased ROS and TNF-α production. Moreover, TNF-α stimulates fatty acid (FA) uptake and lipogenesis in hepatocytes while suppressing FA degradation. Additionally, TNF-α amplifies retinol-binding protein 4 production in hepatocytes, creating a positive feedback loop that exacerbates MASLD[75]. These findings establish a clear pathway by which hepatocyte-derived EVs directly and powerfully impact Kupffer cell behavior.

In addition to Kupffer cells, EVs from lipotoxic hepatocytes also target HSCs, which are key players in liver fibrosis. FA-treated hepatocytes exposed to chemical hypoxia with cobalt chloride (referred to as $CoCl_2$) release elevated levels of EVs enriched with hypoxia-induced cargo. These EVs stimulate profibrotic gene expression in HSCs, promoting fibrosis. *In vivo*, HFD-fed mice exposed to intermittent hypoxia present increased numbers of circulating EVs, which correlate with increased portal inflammation and fibrosis[76]. The exposure of hepatocytes to PA increases EV release and alters their miRNA expression, specifically increasing the levels of miR-192 and miR-122. These modified EVs, when taken up by HSCs, stimulate fibrotic gene expression and promote HSC activation. Notably, EVs carrying miR-128-3p suppress peroxisome proliferator-activated receptor gamma (PPAR-γ) in HSCs, further enhancing profibrogenic gene expression, proliferation, and chemotactic responses. EVs are efficiently internalized by HSCs, a process that relies, at least in part, on the expression of vanin 1 (VNN1) on the EV surface[66]. A study identified miR-1297 as the most upregulated miRNA in PA-treated hepatocytes through miRNA sequencing. EVs derived from these cells induce HSC activation and proliferation. Mechanistically, phosphatase and tensin homolog is a target of miR-1297, and the silencing of phosphatase and tensin homolog leads to HSC activation and proliferation *via* phosphoinositide 3-kinase/AKT signaling[77]. Another key player, miR-107, which is transferred from hepatocyte-derived EVs, activates Wnt signaling in HSCs and IL-9 signaling in $CD4^+$ T cells. In $CD4^+$ T cells, miR-107 suppresses Foxp1, a protein that normally represses IL-9 expression, thereby increasing IL-9 production. This, in turn, activates the Raf/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase pathway in HSCs, further promoting their activation[78]. Moreover, lipotoxic hepatocyte-derived EVs induce a profibrotic and prosenescent phenotype in HSCs characterized by reduced collagen and alpha-smooth muscle actin (α-SMA) expression, increased ROS production, and increased the expression of senescence markers, including IL-6, IL-1β, and p21, and senescence-associated β-galactosidase activity, likely through the AKT-mTOR pathway. Cellular senescence, a state of near-permanent cell cycle arrest, is increasingly recognized as a mechanism for modulating HSC activation. Interestingly, these EVs have also been shown to inhibit HSC activation by inducing senescence. To further elucidate the molecular mechanisms underlying these observations, RNA sequencing profiling of the RNA content of lipotoxic and vehicle-derived hepatocyte EVs revealed significant differences in mRNA and miRNA expression between the two groups[79].

The communication mediated by EVs from lipotoxic hepatocytes extends beyond HSCs, encompassing other cell types involved in MASLD pathogenesis, including endothelial cells and adipocytes. Lipotoxic hepatocyte stress leads to the release of EVs that, when internalized by endothelial cells *via* VNN1, promote angiogenesis and endothelial migration [61]. Furthermore, miR-1-containing EVs suppress Kruppel-like transcription factor 4 a transcription factor that maintains endothelial homeostasis, leading to NF-κB activation and endothelial inflammation. Blocking miR-1 prevents these effects, offering potential therapeutic benefits[80]. Additionally, integrin subunit beta 1-enriched EVs from hepatocytes promote monocyte adhesion to LSECs, facilitating inflammation and fibrosis[81]. Hepatocyte-derived EVs also influence adipose tissue remodeling. HFD consumption upregulates geranylgeranyl diphosphate synthase expression in hepatocytes, increasing Ras-related protein Rab-27A geranylgeranylation and EV secretion. These EVs, enriched with let-7e-5p, drive adipogenesis and lipid accumulation in adipocytes *via* the let-7e-5p-PPAR-g coactivator 1-alpha axis, con-

tributing to systemic metabolic dysfunction[82]. This broad range of EV-mediated communication underscores the systemic impact of hepatocyte-derived EVs.

Immune cell-derived EVs: While hepatocyte-derived EVs play a significant role in the pathogenesis of this disease, the contributions of immune cells are equally substantial. A striking characteristic of MASLD is the infiltration of neutrophils, the primary effectors of innate immunity, into liver tissue. Indeed, the presence of neutrophils is correlated with the progression of the disease[83]. Subsequent investigations revealed intricate mechanisms by which neutrophils modulate the hepatic microenvironment. Specifically, neutrophils contribute by releasing miR-223-enriched EVs to inhibit NLRP3 in proinflammatory macrophages and promote a restorative macrophage phenotype. This, in turn, polarizes macrophages to facilitate the release of IL-10, ultimately reducing HSC activation and collagen deposition[84]. Furthermore, neutrophils release EVs containing ApoE on their surface and carry miR-223. These EVs are preferentially taken up by hepatocytes *via* the hepatocyte LDLR receptor. This transfer of miR-223, which is increased by PA, leads to the suppression of inflammation- and fibrosis-related genes within hepatocytes[55]. Additionally, macrophages, critical players in liver inflammation and fibrosis, have been shown to transfer miRNAs, including miR-223, *via* EVs, influencing diverse cellular processes. Notably, this transfer inhibits HCC cell proliferation and impacts naive monocyte differentiation[85,86]. Macrophage-specific IL-6 signaling triggers the release of miR-223-enriched EVs, which are subsequently internalized by hepatocytes. This process leads to the suppression of miR-223-targeted genes, effectively reducing liver fibrosis. This signaling cascade demonstrates a protective mechanism against fibrosis progression through gene expression modulation in hepatocytes. Consequently, myeloid-specific IL-6 signaling, which stimulates the transfer of antifibrotic miR-223 from macrophages to hepatocytes *via* EVs, presents a potential therapeutic avenue for MASLD[87]. Despite the protective effects observed, the transfer of miR-223 has limitations. Macrophage-derived EVs carrying miR-223 and ApoE also target hepatocytes *via* the LDLR pathway, reinforcing the regulatory role of miR-223 in hepatic inflammation. However, under conditions of lipotoxicity, hepatocytes experience endoplasmic reticulum stress, which downregulates LDLR expression. This reduction in LDLR levels impairs EV uptake, thereby diminishing the protective effects of miR-223 transfer and potentially exacerbating inflammatory and fibrotic responses within the liver[56].

Further investigations revealed the contributions of other miRNAs to MASLD pathogenesis. In both *in vitro* macrophage and HSC cultures, as well as *in vivo* mouse models of carbon tetrachloride-induced fibrosis, in addition to human serum samples, macrophages release EVs enriched with miR-500. When transferred to HSCs, these EVs suppress mitochondrial fusion protein 2 expression, thereby activating the transforming growth factor beta (TGF-β)/small mothers against decapentaplegic signaling pathway and accelerating liver fibrosis. Furthermore, serum EV miR-500 Levels are significantly elevated in patients with advanced liver fibrosis, S1-S4 stages, compared with those with S0 stages[88]. Additionally, Kupffer cells, through EV secretion, transfer miR-690 to hepatocytes and HSCs, thereby regulating crucial processes such as fibrogenesis, inflammation, and lipogenesis. Using an *in vivo* MASH mouse model, the introduction of a miR-690 mimic resulted in significant suppression of MASH characteristics. Conversely, analysis of liver tissue samples from both mouse and human MASH cases revealed a marked deficiency in miR-690 compared with healthy controls, specifically in Kupffer cells and, consequently, in EVs, with Kupffer cell-specific knockout further exacerbating MASH progression. This research identified miR-690 as a key regulator, with its primary target, nicotinamide adenine dinucleotide kinase mRNA, which is inversely correlated with cellular miR-690 Levels[89].

Other cell-derived EVs: In the context of MASLD, other cell-derived EVs play significant roles in disease progression. In obese individuals, visceral adipose tissue secretes EVs that are internalized by hepatocytes, and function as signaling molecules that alter gene expression in the TGF-β pathway. Specifically, these EVs increased tissue inhibitor matrix metalloproteinase 1 and integrin expression while reducing matrix metalloproteinase-7 and plasminogen activator inhibitor 1 Levels in liver cancer cells. In HSCs, these EVs promote the expression of tissue inhibitor matrix metalloproteinase, small mothers against decapentaplegic-3, integrin, and matrix metalloproteinase-9, leading to dysregulation of the extracellular matrix and promoting fibrosis[90]. Similarly, HSCs themselves release EVs carrying phosphorylated platelet-derived growth factor receptor alpha at tyrosine 720 and Src homology 2-containing protein tyrosine phosphatase 2, which, upon interacting with other HSCs, activate them in a paracrine manner, promoting HSC migration and driving liver fibrosis[91]. Previous studies have demonstrated that platelet-derived growth factor and Src homology 2-containing protein tyrosine phosphatase 2 suppress the regulation of development and DNA damage response 1 in HSCs, thereby increasing mTOR signaling, which facilitates the release of EVs. These EVs stimulate the migration of other HSCs, perpetuating profibrotic signals and exacerbating liver fibrosis. Moreover, $CoCl_2$ treatment upregulated DNA damage response 1, and rapamycin administration inhibited mTOR, disrupting this signaling cascade and emphasizing its role in fibrosis progression[92]. Conversely, bone marrow mesenchymal stem cell (MSC)-derived EVs carrying miR-192-5p targeted protein phosphatase 2 regulatory subunit B alpha, effectively inhibiting HSC activation. These findings suggest a potential therapeutic avenue through bone marrow MSC-derived EVs[93]. Similarly, EVs derived from adipose-derived MSCs deliver miR-150-5p, which suppresses CXCL1 expression in HSCs, reducing HSC proliferation and activation and thereby mitigating hepatic fibrosis[94]. Furthermore, MSC-derived EVs transport miR-4465 to HSCs, modulating lysyl oxidase-like protein 2 expression and subsequently alleviating liver fibrosis[95]. These findings highlight the protective role of MSC-derived EVs in liver fibrosis.

Notably, the dysbiotic gut environment significantly influences hepatic pathology through the release of EVs. Specifically, elevated levels of high mobility group box 1 protein are incorporated into EVs within the intestine and released into the circulation. These high mobility group box 1-enriched EVs travel to the liver, where they induce hepatic steatosis [96]. Furthermore, microbiota-derived DNA carried within these EVs acts as a critical pathogenic factor, activating the cyclic guanosine monophosphate–adenosine monophosphate synthase/stimulator of interferon genes signaling pathway upon internalization by hepatocytes and HSCs, thus promoting hepatic inflammation and fibrosis. Importantly, V-set and

immunoglobulin domain-containing 4-positive macrophages exert a protective function by clearing these pathogenic EVs *via* complement-mediated opsonization, effectively preventing their accumulation within liver cells[97].

Collectively, EVs emerge as pivotal mediators in MASLD pathogenesis, facilitating intercellular communication among lipotoxic hepatocytes, macrophages, Kupffer cells, HSCs, endothelial cells, and adipocytes. These EVs carry a complex cargo of miRNAs, lipids, and proteins that orchestrate inflammatory and fibrotic responses. While lipotoxic hepatocyte-derived EVs contribute to MASLD/MASH progression, immune cell-derived EVs exert protective effects by transferring regulatory molecules to hepatocytes, ameliorating disease progression. Further exploration of EV biogenesis, cargo selection, and uptake mechanisms would provide critical insights into MASLD pathogenesis and uncover novel therapeutic targets.

EVS IN MASLD-ASSOCIATED COMPLICATIONS

EVs and hepatic fibrosis/cirrhosis

MASLD progresses through different stages after liver steatosis by fibrosis development and eventually results in cirrhosis[98,99]. The activation of HSCs plays a role in liver fibrosis by increasing EV production and altering their proteomic profile. Additionally, EVs from activated HSCs are linked to extracellular matrix remodeling, proliferation, and migration[100]. Hepatocyte-derived EVs contribute to fibrosis in MASLD through multiple mechanisms. EVs released from hepatocytes stimulate HSCs through the hypoxia signaling pathway. This activation is mediated by iron accumulation in an ROS-dependent manner, arising from mitochondrial oxidative stress and ultimately leading to hepatocyte inflammation[74,101]. EVs containing VNN1 from hepatocytes contribute to the internalization process in HSCs. These EVs influence the LX-2 cell line by inducing HSC activation and decreasing the levels of regulators of quiescent HSCs, such as PPAR-γ. This process aligns with changes observed in liver endothelial cells, leading to angiogenesis and aggravating MASH, which is more severe than MASLD[61,102]. PPAR-γ participates in macrophage polarization, activating the Toll-like receptor 4/NF-κB pathway, which contributes to lipid dysregulation and inflammation[74,101]. Moreover, some EVs play roles in the dysregulation of the mitophagy pathway, which plays a vital role in clearing dysfunctional mitochondria. These EVs, such as those containing the miR-27A and LIM domain and actin binding 1, downregulate the expression of putative protein kinase 1, which is a key modulator of mitophagy[103,104]. In addition to hepatocytes, other cell types, such as adipocytes, can also incorporate their EVs into HSCs, possibly causing cellular dysregulation. EVs secreted by adipocytes in obese individuals might affect the regulation of TGF-β, a vital component of fibrosis, after incubation with hepatic cell lines[90].

EVs and HCC

MASLD has manifestations that can lead to disease progression and result in HCC[105]. Modifications in EV content during MASLD progression can influence HCC onset and progression[106]. In patients with MASLD, elevated levels of miR-504-3p-enriched EVs have been observed[107]. These EVs facilitate HCC progression by modulating frizzled class receptor 7, thereby inhibiting Wnt/β-catenin signaling and enhancing tumor-associated characteristics[108]. One of the mechanisms driving HCC progression is the polarization of tumor-associated macrophages. EVs derived from HCC cells enriched with miR-21-5p modulate macrophage polarization by influencing the specificity protein 1/X-box binding protein 1 pathway[109]. Higher levels of miR-21-5p were observed in patients with MASLD, with a progressive increase observed in more severe stages of the disease[110]. Recently, five EV-miRNAs, specifically miR-19-3p, miR-16-5p, miR-223-3p, miR-30d-5p, and miR-451a, have been identified as promising biomarkers for MASLD-related HCC. Among these, miR-19-3p has the highest diagnostic accuracy, particularly for early-stage and patients lacking alpha-fetoprotein, indicating its potential for both diagnosis and prognosis[59].

EVs and cardiovascular complications

Following MASLD, patients are at high risk of developing CVDs, which stem from cardiometabolic imbalances and may result in death[111,112]. Recent findings have even highlighted a potential link between MASLD and nonischemic etiologies of sudden cardiac death (SCD). A study investigating post-mortem findings in adults experiencing SCD revealed a higher prevalence of MASLD among individuals of Hispanic ethnicity and a lower prevalence of coronary artery disease in this group. Given the increasing burden of MASLD, these ethnicity-based disparities and the specific nature of nonischemic SCD warrant immediate and in-depth investigation, underscoring the systemic ramifications of this liver disease[113]. One key mechanism through which MASLD influences the cardiovascular (CV) system involves the release of EVs carrying miRNAs from steatotic hepatocytes. For example, miRNA-containing EVs such as miR-1 from hepatocytes contribute to atherogenesis by altering Kruppel-like transcription factor 4 in the NF-κB axis, affecting smooth and cardiac muscle development and promoting inflammation in vein endothelial cells[80]. MASLD is also linked to atherosclerosis progression. EVs derived from steatotic hepatocytes carrying miRNA-30a-3p suppress ATP binding cassette subfamily A 1, restricted cholesterol removal to apolipoprotein A-I, and contributed to foam cell buildup in blood vessels[114]. Endothelial hyperpermeability in MASLD is caused by high levels of miRNA-7 EVs, which lead to lysosome-associated membrane protein 1 Lysosomal permeabilization, activate the cathepsin B/NLRP3 inflammasome pathway, and drive inflammation, which contributes to coronary microvascular dysfunction[115]. Moreover, CVD might arise from disruptions in the ceramide-related pathway caused by acid ceramidase depletion, leading to lysosomal ceramide accumulation and MASLD. EV levels subsequently increase and activate the NLRP3 inflammasome, ultimately causing endothelial injury in the carotid arteries of mice[116].

In addition to the molecular mechanisms involving circulating factors such as EVs and miRNAs, these vesicles also play a significant role in mediating histological and tissue-level changes that contribute to CV complications in MASLD. Indeed, EVs released in the context of MASLD are pivotal in driving these complications by inducing significant alterations, particularly in the heart and blood vessels. These EVs contribute to endothelial dysfunction by impairing nitric oxide production and increasing oxidative stress, affecting the proper dilation and constriction of blood vessels[113,117,118]. Furthermore, they can alter cardiomyocyte function, leading to decreased survival, reduced contractility, and increased fibrosis, thereby increasing the risk of heart failure and arrhythmias[119,120]. The pro-fibrotic signals carried by EVs promote the development of fibrosis in both the liver and the heart, exacerbating MASLD progression and stiffening the heart muscle[121]. By delivering inflammatory molecules, EVs also contribute to systemic inflammation, further damaging the endothelium. Additionally, EVs influence vascular structure and function, potentially leading to detrimental remodeling and narrowing of blood vessels[122]. These diverse effects are mediated through mechanisms such as lipid accumulation, the promotion of oxidative stress, and the alteration of cellular signaling pathways in target cells within the CV system, ultimately establishing a strong link between MASLD and an elevated risk of CV events.

EVs and other extrahepatic complications

The influence of EVs in MASLD extends beyond the CV system, impacting a range of extrahepatic organs, including the pancreas, colon, and nervous system[123]. This underscores the systemic nature of MASLD and the far-reaching consequences of EV-mediated signaling. In the context of type 2 diabetes, a common comorbidity of MASLD, hepatocyte-derived EVs play a significant role in modulating pancreatic beta cell function. Specifically, these EVs promote beta cell proliferation and insulin production. For example, miR-7218-5p, carried within EVs, regulates beta cell survival through the CD74 pathway, leading to the overproduction of insulin[124]. Conversely, chronic obesity, a condition often associated with MASLD, led to decreased miR-3075 expression in murine hepatocytes. This reduction impacted glucose uptake. Concurrently, the upregulation of miR-434-3p forced M1 macrophage polarization and insulin resistance[125]. In addition to contributing to glucose homeostasis dysregulation, hepatocyte-derived EVs, such as those carrying miR-130a-3p, modulate the AKT-AS160-glucose transporter type 4 pathway. This modulation occurred through the inhibition of PH domain leucine-rich repeat protein phosphatase 2, thereby affecting glucose transporter type 4 activity[126]. In addition to metabolic regulation, the role of the liver in neuronal support is also impacted by EVs in MASLD. The liver secretes selenoprotein P (SELENOP) to provide selenium to neurons, a crucial process for neuronal function. However, this liver-neuron interaction was diminished in patients with MASH compared with healthy individuals[127]. SELENOP uptake is mediated by ApoE receptor 2. Dysregulation of this pathway causes SELENOP deficiency, which contributes to neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease through amyloid β-triggered cell death[128]. Furthermore, the influence of EVs in MASLD extends to cancer metastasis, a critical clinical concern. In MASLD, EVs from fatty liver can drive colorectal cancer metastasis to the liver by inducing Yes-associated protein activity in the Hippo pathway, a critical regulator of tumorigenesis. Notably, EVs carrying miR-25, miR-92, or miR-103 enhanced this effect. The activation of Yes-associated protein stimulates cysteine-rich angiogenic inducer 61 expression, leading to colorectal cancer cell migration and M2 tumor-associated macrophage recruitment, ultimately resulting in liver metastasis[129]. These diverse extrahepatic effects underscore the critical role of EVs in mediating the systemic complications of MASLD, highlighting their potential as therapeutic targets.

EVS AS BIOMARKERS FOR MASLD

EV-based liquid biopsies

The limitations of existing noninvasive diagnostics for MASLD and MASH, which rely on imaging-based methods and multiple algorithm tests, have been recognized. While techniques such as magnetic resonance elastography and transient elastography (TE) offer high diagnostic accuracy, magnetic resonance elastography is costly, and TE lacks specificity for MASH-associated fibrosis[130]. Other ultrasound-based elastography methods, such as point shear wave elastography and two-dimensional shear wave elastography, exhibit similar diagnostic capabilities[131]. Multiple algorithms include direct commercial assays such as the "enhanced liver fibrosis panel" test, the Fibro Test, and procollagen III N-terminal peptide, as well as indirect indices such as the fibrosis-4 index, the aspartate aminotransferase-to-platelet ratio index, and the MASLD fibrosis score. However, these tests were originally developed for hepatitis C-related fibrosis and have been repurposed for MASLD, leading to inconsistent diagnostic performance and a need for more specific and reliable biomarkers[132,133]. The invasiveness and expense of liver biopsies, the gold standard, limit their applicability for screening. Therefore, researchers have focused on developing noninvasive biomarkers based on liquid biopsy methods involving the analysis of molecules in body fluids such as blood. Elevated serum alanine aminotransferase levels detect MASLD with high sensitivity but not MASH, whereas increased cytokeratin 18 in circulation indicates MASH in patients with MASLD[134].

EVs serve as promising biomarkers for MASLD by carrying lipids, proteins, miRNAs, and lncRNAs, reflecting pathological alterations in liver metabolism and inflammation[135]. The diverse cargo of EVs, which is influenced by their cellular origin and physiological/pathological state, prompted exploration of their potential for tracking disease progression and therapeutic response. A pivotal study, which analyzed patient-derived EVs, confirmed the diagnostic potential of EV proteins by identifying refined biomarker panels, comparing EV proteomes from patients with cancer to those from healthy individuals, and differentiating between cancer types[136]. In the context of MASLD, a study showed that patients with MASLD or MASH presented with significantly elevated levels of EVs derived from invariant natural killer T cells and macrophages/monocytes. These elevated EV levels correlated with alanine aminotransferase levels and

the histological severity of MASH. In line with this, the levels of these EVs effectively distinguished between patients with MASLD/MASH and patients with chronic hepatitis C, achieving a high degree of accuracy, as indicated by an area under the receiver operating characteristic curve (AUROC) of 0.99[137].

Lipid-based EV diagnosis

EV-associated lipids have been particularly investigated as biomarkers, given the close link between MASLD and lipid metabolism. A study demonstrated an increase in C16: 0 ceramide-containing EVs in both murine models and human subjects with MASH[36]. Further exploration of urinary EVs from patients with MASLD and MASH revealed a lipidomic signature comprising four lipid molecules - FFA (18:0), lysophosphatidylcholine (22:6/0:0), FFA (18:1), and phosphatidylinositol (16:0/18:1) - that effectively differentiated MASH with an AUROC of 92.3%[138]. Subsequent studies also revealed that the quantity of hepatocyte-derived EVs, identified by cytochrome P450 2E1-positive and asialoglycoprotein receptor-positive ($ASGR^+$) markers, increased in patients with MASLD and subsequently decreased with disease resolution following bariatric surgery. Furthermore, these hepatocyte-derived EVs were correlated with the severity of steatosis and inflammation in patients with MASH and with steatosis in patients with MASLD. Importantly, a reduction in sphingolipid levels within these EVs, specifically ceramides, dihydroceramides (20:0), and S1P, was associated with weight loss. A multivariable regression model that integrates EVs, body mass index, sphingosine, and dihydroceramide effectively discriminated between patients with and without MASLD, yielding an AUROC of 0.80[139]. Collectively, these findings suggest that lipid-laden EVs hold promise as noninvasive diagnostic and staging tools for MASLD.

Protein-based EV biomarkers

Proteomic analysis of EV proteins reveals their potential as biomarkers in MASLD. Liquid chromatography-mass spectrometry/mass spectrometry analysis of EVs from human serum samples revealed various liver diseases, identifying alpha-2-macroglobulin for alcoholic hepatitis and apolipoprotein C3 for MASLD as significantly upregulated proteins [140]. A study indicated that the levels of hepatocyte-specific markers, such as ASGR1, were significantly higher in patients with cirrhotic MASH[62]. A slow off-rate modified aptamer protein array identified seven circulating EV proteins - Wnt-induced secreted protein 1, aminoacyl-tRNA synthetase complex-interacting multifunctional protein 1, IL-27 receptor alpha subunit, intercellular adhesion molecule 2, IL-1β, serine/threonine kinase 16, and repulsive guidance molecule A - that were increased in precirrhotic and cirrhotic MASH samples compared with healthy controls, suggesting their potential for MASH diagnosis[62]. Proteomic analyses initially revealed eight candidate proteins, among which fibulin-3 and fibulin-1 exhibited significant alterations in advanced fibrosis. Subsequent validation confirmed that only fibulin-3 Levels were significantly elevated in patients with advanced fibrosis, distinguishing them from those with nonadvanced fibrosis. Furthermore, fibulin-3, but not fibulin-1, independently predicts liver-related events, with AUROC values of 0.727, 0.761, and 0.726 at 3 years, 5 years, and 7 years, respectively, establishing it as a promising biomarker for MASLD risk stratification[141]. Further analyses of EV protein cargo in plasma samples from healthy controls, patients with MASLD, and patients with MASH revealed that hepatogenic EVs carrying glucose transporter 1 were highly indicative of MASLD. Notably, glucose transporter 1-derived EVs exhibited an AUROC of 0.85 for MASLD diagnosis, which further improved to 0.91 when combined with the fibrosis-4 index score, demonstrating their potential as early diagnostic markers[142].

miRNA-based EV biomarkers

MiRNAs carried by EVs have been extensively investigated for their potential as MASLD biomarkers. The diagnostic performance of EV-derived miRNAs in MASLD has been previously reviewed[143]. Recent evidence specifically highlights the role of EV-derived miRNAs as biomarkers in patients with MASLD. For example, a study analyzing serum samples from patients with chronic hepatitis C and healthy controls identified a nine-miRNA signature (miR-1225-5p, miR-1275, miR-638, miR-762, miR-320c, miR-451, miR-1974, miR-1207-5p, and miR-1246) that effectively differentiated liver diseases, including MASH, from healthy controls, with specific miRNAs reflecting the extent of liver fibrosis and inflammation[144]. Among the most studied miRNAs, miR-122, a liver-specific miRNA, is widely established as a biomarker of liver diseases[145]. A recent study demonstrated that analyzing miRNAs within EVs, particularly miR-122 (AUROC = 0.79), provided more accurate differentiation between individuals with MASLD and healthy controls than examining total serum miRNAs. The enrichment of miR-122 and miR-192 in circulating EVs, coupled with their depletion in liver tissue, suggested active EV-mediated transfer of these molecules, potentially contributing to systemic disease propagation[145]. Furthermore, investigations analyzing miR-122, miR-192, and miR-128-3p revealed that miR-128-3p exhibited high diagnostic potential for MASLD, with the highest AUROCs for total cell-free RNA, global EVs, and liver-specific ($ASGR1^+$) EVs (0.92, 0.89, and 0.80, respectively)[146]. Distinct miRNA patterns have been observed in both mice and humans with MASLD, with decreases in the expression of miR-135a-3p, miR-129b-5p, and miR-504-3p and increases in the expression of miR-122-5p in circulating EVs and serum samples. Notably, miR-135a-3p within circulating EVs has strong diagnostic potential for MASLD, with an AUROC of 0.85[107]. Additionally, miR-192-5p was significantly elevated in the serum of patients with MASLD and MASH, which was strongly correlated with liver damage markers and hepatic steatosis severity[71]. Finally, in a cohort with MASLD-related HCC, miR-223-3p was significantly upregulated in plasma EVs from patients compared with healthy controls, highlighting its potential as a biomarker in this specific context[59].

However, a crucial point to consider is that miRNAs, while promising for both diagnosis and treatment, encounter obstacles because of their relatively low specificity. This lack of precise targeting can impede their successful translation into routine clinical practice. The challenge lies in the fact that a single miRNA can interact with multiple mRNAs, making it difficult to pinpoint and modulate a specific biological pathway with the accuracy needed for effective diagnosis and targeted therapies[147,148]. To address this, researchers are actively pursuing strategies such as developing

targeted delivery systems, designing more specific miRNA molecules, and utilizing miRNA panels to identify unique disease expression patterns. Crucially, rigorous validation of miRNA-mRNA interactions is essential to ensure the functional relevance of identified targets, ultimately aiming to balance the broad regulatory potential of miRNAs with the need for precise clinical interventions[147].

lncRNA-based EV biomarkers

lncRNAs, a diverse class of noncoding RNAs ranging from over 200 base pairs to 100 kilobases, play crucial roles in regulating gene expression, notably by acting as miRNA sponges to control mRNA levels. Previous research has demonstrated a strong association between lncRNAs and various pathophysiological conditions, including liver diseases and MASLD. RNA sequencing of samples from patients with liver fibrosis and MASLD has revealed distinct lncRNA expression profiles[149-151], revealing differential expression patterns in MASLD samples compared with control samples. These dynamic alterations in lncRNA expression are linked to the development and progression of MASLD. Recent systematic reviews highlight the altered expression of noncoding RNAs in MASLD, identifying lncRNAs such as nuclear paraspeckle assembly transcript 1 (NEAT1), maternally expressed gene 3 (MEG3), and mucosa-associated lymphoid tissue lymphoma translocation protein 1 as promising diagnostic biomarkers in MASLD. Specifically, several lncRNAs, such as HOX transcript antisense RNA, H19, Gm15622, and NEAT1, are upregulated, whereas others, such as MEG3, are downregulated[152,153]. Functional studies have elucidated the roles of these lncRNAs in MASLD pathogenesis; for example, NEAT1 exacerbates lipid accumulation by modulating the c-Jun/sterol regulatory element-binding protein 1 (SREBP-1c) axis through miR-139-5p sponging[154], HOX transcript antisense RNA regulates lipid accumulation *via* the miR-130b-3p/rho-associated, coiled-coil-containing protein kinase 1 axis[155], H19 promotes hepatic lipogenesis by directly targeting the miR-130a/PPAR-γ axis[156], Gm15622 stimulates SREBP-1c expression and lipid accumulation by sponging miR-742-3p[157], NEAT2 facilitates hepatic steatosis and insulin resistance by enhancing nuclear SREBP-1c stability[158], and MEG3 upregulates sirtuin 6 by ubiquitinating enhancer of zeste homolog 2[159]. Although these findings suggest the potential of lncRNAs as biomarkers in MASLD, their verification in larger cohorts and further functional characterization are still necessary.

In summary, EVs hold considerable promise as biomarkers in MASLD, which makes them attractive candidates for noninvasive liquid biopsies, potentially offering earlier and more accurate diagnoses than traditional methods do. However, despite this potential, the translation of EV-based biomarkers into routine clinical practice faces significant limitations. One major hurdle is the variability in EV isolation and analysis methods, leading to low sensitivity and specificity in diagnostic tests. The absence of standardized protocols for EV isolation, characterization, and cargo analysis has contributed to inconsistent results across studies[160]. Moreover, the lack of commercially available clinical test kits hinders their widespread adoption and application. Critically, many candidate biomarkers identified in smaller studies lack robust validation in large, diverse patient cohorts. This raises concerns about their generalizability and clinical utility [161]. Without large-scale verification, the true diagnostic and prognostic value of these biomarkers remains uncertain. Furthermore, the complexity of MASLD, which involves multiple cell types and pathways, necessitates a comprehensive approach that considers a panel of biomarkers rather than relying on a single marker. This adds to the challenge of developing reliable and clinically applicable EV-based diagnostic tools[162,163].

EV-BASED THERAPEUTIC STRATEGIES FOR MASLD

While significant progress has been made in MASLD drug therapies, with novel agents such as thyroid hormone receptor beta, farnesoid X receptor, PPAR, sodium-glucose cotransporter-2, and glucagon-like peptide-1 receptor agonists demonstrating efficacy in clinical trials, challenges remain[164]. Current pharmacological approaches often target specific disease stages, such as inflammation, fat accumulation, and fibrosis, and synthetic drugs can pose risks due to off-target effects[165]. Furthermore, surgical interventions, while effective in select cases, require careful patient selection and carry inherent risks[166]. Even promising small interfering RNA-based therapies face hurdles in terms of delivery, pharmacokinetics, and side effect profiles[167]. These limitations underscore the urgent need for innovative therapeutic strategies that offer improved targeting and reduced systemic toxicity.

In response to these limitations, EVs have emerged as a highly promising avenue for targeted MASLD treatment. These naturally occurring, membrane-bound nanoparticles offer a unique advantage by shielding their molecular cargo from degradation within biological environments. As inherent carriers, EVs can effectively transport therapeutic payloads directly to the site of action, encompassing a diverse range of molecules, such as proteins, lipids, miRNAs, and nucleic acids[168]. Notably, EVs derived from stem cells also have the potential to stimulate cellular regeneration[169]. The ability of EVs to interact with specific target organs or receptors stems from their unique surface protein barcodes and adaptable bimolecular coronas. This versatility allows for the encapsulation and delivery of various therapeutic agents, including nucleic acids, chemotherapeutic drugs, small molecules, and even viruses, to precise locations[168,169]. The biocompatibility, low immunogenicity, capacity to traverse biological barriers, and adaptable cargo loading of EVs make them highly attractive therapeutic vehicles[168]. Future EV-based therapies aim to leverage these properties by loading them with specific therapeutic cargo or drugs, ensuring targeted delivery and minimizing off-target effects. Consequently, the cargo-specific therapeutic effects and site-specific actions facilitated by protein barcoding position EVs as compelling candidates for developing novel therapeutic modalities across a spectrum of diseases, including MASLD[170].

Given the inherent potential of EVs as therapeutic tools, distinguishing between their two primary modes of application is crucial: As delivery vehicles and as therapeutic agents[171]. This functional distinction leads to a classification into two main categories: Naturally occurring EVs and engineered EVs[44]. Naturally occurring EVs, derived

from cells such as immune cells and MSCs, carry endogenous cargo that reflects their cellular origin, endowing them with inherent therapeutic capabilities. Conversely, engineered EVs undergo modifications through biological or chemical methods, including surface alterations and physical or biological treatments, to facilitate the loading of specific therapeutic cargo[172]. While various loading techniques exist, the selection of an appropriate method is critical for efficient cargo encapsulation and depends on factors such as the physicochemical properties of the cargo, its source, and the EV subtype[172]. The diverse applications of EVs as both "delivery vehicles" and "therapeutic agents" are well supported by studies across a range of diseases, highlighting their versatility and potential in therapeutic development [168].

Preclinical studies: Harnessing EVs for targeted MASLD therapy

A crucial advantage of using EVs as therapeutic delivery vehicles lies in their inherent ability to protect their cargo from degradation within the complex biological milieu[173]. The lipid bilayer membrane of EVs acts as a robust barrier, effectively shielding encapsulated molecules such as proteins, nucleic acids, and small-molecule drugs from enzymatic breakdown, oxidation, and other forms of degradation. This protection is critical, as many therapeutic agents are susceptible to rapid degradation in circulation or within cellular compartments, limiting their bioavailability and efficacy [174]. By encapsulating these agents within EVs, we can significantly increase their stability and ensure that they reach their target sites intact.

Furthermore, the EV membrane is not merely a passive barrier. A variety of surface proteins that contribute to vesicle stability and functionality have been studied[175]. These proteins can modulate the interaction of EVs with their environment, influencing factors such as cellular uptake and intracellular trafficking. Additionally, the internal environment of EVs can be carefully controlled during loading, ensuring optimal conditions for the stability and activity of the therapeutic cargo. For example, maintaining an appropriate pH or redox potential within the EV lumen can prevent degradation or premature activation of encapsulated enzymes or drugs[176]. This sophisticated level of protection and control makes EVs highly promising platforms for delivering sensitive therapeutic agents to specific cells and tissues, particularly in challenging disease contexts such as MASLD.

EVs delivering miRNAs to target fibrosis in MASLD

HSCs are central to the progression of liver fibrosis, a critical aspect of MASLD. EVs offer a promising avenue for delivering therapeutic miRNAs that can modulate HSC activity and reduce collagen production. In a dietary-induced mouse model of MASH characterized by steatosis, inflammation, and fibrosis, EVs isolated from human HepG2 hepatocytes displayed notable therapeutic efficacy[177]. Administering these EVs, either as preventive measures or as treatments, led to a substantial reduction in hepatic fibrosis, as evidenced by decreased collagen deposition and α-SMA expression. This is accompanied by a reduction in hepatic inflammation. Mechanistically, these EVs transport a collection of 205 miRNAs, with seven prominent species (miR-423-5p, -483-5p, -191-5p, -148a-3p, -423-3p, -92a-3p, and -122-5p) predicted to directly target genes involved in fibrosis. These findings highlight the potential of EVs, particularly those originating from hepatocytes, as effective vehicles for delivering antifibrotic miRNAs, suggesting a novel therapeutic approach for MASLD-associated fibrosis.

In addition to the role of hepatocyte-derived EVs in MASLD, recent studies have investigated the direct impact of EVs released from steatotic hepatocytes on HSC behavior. Specifically, research employing primary rat hepatocytes, where steatosis was induced *via* FFAs, demonstrated that EVs originating from these lipid-laden cells (FFA-EVs) significantly suppressed the expression of collagen type 1 and α-SMA in early-stage activated HSCs[79]. This suppression coincided with an increase in ROS production and the promotion of senescence markers, including IL-6, IL-1β, and p21, and senescence-associated β-galactosidase activity within HSCs through the modulation of the AKT-mTOR signaling cascade. Analysis of EV RNA content revealed distinct profiles between those derived from normal and steatotic hepatocytes, underscoring the critical role of the FFA-EV cargo in altering HSC characteristics. These findings suggest that EVs from steatotic hepatocytes may actively regulate fibrosis progression in MASLD by triggering HSC senescence, thereby presenting potential new avenues for therapeutic intervention.

In addition to the direct impact of hepatocyte-derived EVs, the role of LSECs in modulating MASLD-related fibrosis is emerging. LSECs, which are critical for maintaining hepatic microcirculation and nutrient exchange, exert paracrine effects through the release of EVs[178]. Research indicates that LSEC-derived EVs can significantly attenuate the activation of HSCs by reducing the expression of activation markers and suppressing HSC proliferation. Interestingly, these EVs also suppress inflammatory gene expression in Kupffer cells. These findings suggest that LSEC-derived EVs play a complex regulatory role in the MASLD microenvironment, effectively dampening the fibrogenic phenotype of HSCs and modulating the inflammatory response of Kupffer cells. These findings position LSEC-derived EVs as promising therapeutic candidates for MASLD, suggesting a novel approach to simultaneously target multiple cell types involved in disease progression. Furthermore, the distinct effects of these EVs on different cell populations may also hold diagnostic potential in monitoring MASLD.

EV delivery of anti-inflammatory effects in MASLD

Building upon the exploration of EV-based therapies in MASLD, a significant area of interest lies in their capacity to modulate macrophage polarization, a key factor in disease progression. Given the limited availability of effective treatments for MASH, the therapeutic potential of human umbilical cord MSC derived EVs (huc-MSC-EVs) has been investigated[179]. Research employing a Western diet-induced MASH mouse model demonstrated that huc-MSC-EV administration effectively mitigated liver steatosis, inflammation, and fibrosis while also improving metabolic parameters. Notably, these EVs reduce hepatic macrophage accumulation and promote a shift toward M2 macrophage polarization, a phenotype associated with tissue repair and resolution of inflammation, over the proinflammatory M1

phenotype. Mechanistically, the observed effects are attributed, at least in part, to the high expression of miR-24-3p within huc-MSC-EVs, which target the cyclic guanosine monophosphate–adenosine monophosphate synthase/stimulator of interferon gene in macrophages, thereby regulating their polarization. The overexpression of this miRNA amplified the therapeutic benefits of the EVs, suggesting a critical role for miR-24-3p in mediating their effects. These findings highlight the potential of huc-MSC-EVs to ameliorate MASH by modulating macrophage polarization through miR-24-3p delivery, suggesting a promising avenue for clinical translation.

Continuing the exploration of the use of MSC-EVs in MASLD treatment is crucial to address the complex role of macrophage polarization. While the preceding study highlighted the beneficial shift toward M2 macrophage polarization in mitigating MASH, concerns exist regarding the potential profibrotic nature of M2 macrophages, which could theoretically exacerbate liver fibrosis. However, evidence suggests that MSC-EVs can alleviate HFD-induced MASH despite this concern[180]. To further investigate this matter, researchers confirmed the M2-polarizing capacity of their MSC-EV preparations *in vitro* before testing them in a MASH mouse model. Surprisingly, compared with the control treatment, treatment with MSC-EVs resulted in a reduction in MASLD activity scores and liver fibrosis. Although an increase in $CD163^+$ M2 macrophages was observed in the liver, along with a reduction in serum IL-6 Levels, the overall outcome indicated that MSC-EV therapy was effective in reducing liver fibrosis. These findings suggest that while MSC-EVs do induce M2 macrophage polarization, their net effect in the context of MASH is antifibrotic, possibly due to other concurrent immunomodulatory mechanisms. These findings underscore the need for a nuanced understanding of macrophage polarization in EV-mediated therapies for MASLD, where the balance of pro- and antifibrotic signals ultimately determines the therapeutic outcome.

While previous research has highlighted the potential of MSC-EVs in modulating macrophage polarization to alleviate inflammation in MASLD, alternative strategies leveraging the targeted delivery of anti-inflammatory agents *via* EVs are also being explored. Recognizing the pivotal role of proinflammatory cytokines, such as TNF and IL-1β, in MASH pathogenesis, researchers have investigated the feasibility of inhibiting their expression in hepatic macrophages *via* EV-mediated delivery[181]. Given that intravenously administered EVs accumulate primarily in the liver and are readily taken up by hepatic macrophages, this approach holds promise for targeted therapeutic intervention. In this study, antisense oligodeoxynucleotides (ASOs) targeting TNF-α (ASO-TNF) and 2-deoxy-D-glucose (2DG) were used to suppress TNF-α and IL-1β expression in macrophages. EVs loaded with ASO-TNF-α or 2DG effectively reduce the expression of these inflammatory cytokines both *in vitro* and *in vivo*. Furthermore, the administration of these EV-loaded agents significantly attenuated experimental steatohepatitis in murine models of MASH. Mechanistically, RNA sequencing revealed that treatment with EV-delivered ASO-TNF-α or 2DG inhibited proinflammatory signaling pathways and upregulated the expression of superoxide dismutase 1, an antioxidant enzyme. These findings demonstrate that EV-mediated delivery of anti-inflammatory agents, such as ASO-TNF and 2DG, can effectively alleviate experimental steatohepatitis by directly targeting inflammatory pathways in hepatic macrophages, suggesting a promising therapeutic avenue for MASH treatment.

EV delivery of therapeutics to target lipid metabolism in MASLD

In addition to the immunomodulatory effects of EVs, particularly in terms of macrophage polarization, another promising avenue for MASLD therapy involves directly targeting lipid metabolism. Given the central role of lipid accumulation in the pathogenesis of MASLD, the potential of MSC-EVs to modulate this process has been explored. A recent study investigated whether MSC-EVs could inhibit hepatocyte lipid accumulation by regulating mitochondrial fission, a process implicated in steatosis[182]. Using both lipotoxic hepatocytes *in vitro* and an HFD-induced MASLD mouse model, researchers have shown that MSC-EV treatment effectively reduces the expression of dynamin-related protein 1 (DRP1), a key regulator of mitochondrial fission. This downregulation of DRP1 Led to a reduction in mitochondrial fission, mitochondrial damage, and subsequent lipid deposition in hepatocytes and liver tissues. Mechanistically, a study revealed that RING finger protein 31 (RNF31), which is transported by MSC-EVs, plays a crucial role in mediating the inhibitory effect on DRP1. RNF31 suppressed DRP1 expression and mitochondrial fission, thereby ameliorating mitochondrial dysfunction and reducing hepatocyte lipid accumulation. These findings suggest that MSC-EVs can effectively target DRP1-mediated mitochondrial fission through RNF31 delivery, suggesting a novel approach to inhibit hepatocyte steatosis and potentially halt the progression of MASLD.

To further explore the therapeutic potential of MSC-EVs for MASLD, researchers have investigated their role in regulating lipid homeostasis. A recent study elucidated the mechanisms by which MSC-EVs influence lipid accumulation [183]. The use of OA-treated hepatic cells and a HFD-induced MASLD mouse model demonstrated that MSC-EVs effectively promoted FA oxidation and reduced lipogenesis. Nontargeted lipidomic and transcriptome analyses revealed a positive correlation between MSC-EV treatment and the phosphorylation of AMP-activated protein kinase. Through MSC-EVs and gene manipulation experiments, calcium/calmodulin-dependent protein kinase 1, which is transferred *via* MSC-EVs, was shown to ameliorate lipid accumulation in an AMP-activated protein kinase-dependent manner. This mechanism involves the inhibition of SREBP-1c-mediated FA synthesis and the enhancement of PPAR-α-mediated FA oxidation. These findings highlight the therapeutic potential of MSC-EVs in preventing HFD-induced MASLD by regulating lipid homeostasis through the delivery of calmodulin-dependent protein kinase 1, suggesting a promising strategy for combating liver steatosis.

In addition to the inherent therapeutic capabilities of MSC-EVs, recent investigations have explored strategies to further augment their efficacy in treating MASLD. One such approach involves preconditioning MSCs with curcumin (Cur), a natural compound known for its anti-inflammatory and immunomodulatory properties[184]. Researchers have hypothesized that, compared with standard MSC-EVs, EVs derived from Cur-preconditioned MSCs (MSC-EVs-Cur) would exhibit superior therapeutic effects. Compared with treatment with MSC-EVs-Cur alone, treatment with MSC-EVs-Cur significantly ameliorated steatosis and inflammation in a methionine/choline-deficient diet-induced MASH

mouse model, as evidenced by reduced fibrosis; decreased serum liver enzyme, triglyceride, and cholesterol levels; and increased lipid peroxidation. Notably, these beneficial effects persisted for 3 months after treatment in the MSC-EV-Cur group, whereas MASH features recurred in the MSC-EV group. *In vitro* studies using PA-treated HepG2 cells corroborated these findings, demonstrating that MSC-EVs-Cur effectively reversed lipotoxicity and oxidative stress. Mechanistically, MSC-EVs-Cur regulated key inflammatory and oxidative stress markers, genes involved in liver fibrogenesis, and lipid synthesis and transport. Importantly, compared with MSC-EVs, MSC-EVs-Cur significantly downregulated the ASK-c-Jun N-terminal kinase-B-cell lymphoma 2- associated X protein genes, which are implicated in mitochondrial stress and apoptosis. These results suggest that Cur preconditioning enhances the therapeutic potential of MSC-EVs in MASH, offering a promising strategy to not only ameliorate but also prevent the recurrence of this complex liver disease by modulating crucial pathways involved in inflammation, oxidative stress, and mitochondrial function.

Research on the therapeutic potential of stem cell-derived EVs in mitigating MASLD has also explored the effects of EVs from stem cells of the apical papilla (SCAPs). In one study utilizing an HFD-induced MASH mouse model and oleic acid/PA-treated HCC cells *in vitro*, SCAP-derived EVs significantly reduced weight gain and liver damage while alleviating hepatic fat accumulation[185]. Mechanistically, these EVs promote the expression of genes involved in FA oxidation and transport and concurrently suppress genes associated with FA synthesis. Additionally, they reduced the serum inflammatory cytokine levels and hepatic inflammatory marker expression. Similarly, in a separate study employing a methionine/choline-deficient diet-induced MASH mouse model, intravenous administration of SCAP-derived EVs at varying concentrations led to significant reductions in body weight loss and liver damage, along with a marked decrease in hepatic fat accumulation[186]. These findings collectively underscore the capacity of SCAP-derived EVs to modulate lipid metabolism and inflammatory responses in MASLD, reinforcing the potential of stem cell-derived EV therapy as a promising strategy for this complex liver disease.

The promising therapeutic potential of EVs in addressing various facets of MASLD is evident, particularly their ability to target fibrosis, modulate macrophage polarization, and regulate lipid metabolism. Compared with traditional drug delivery methods, EVs offer distinct advantages, including enhanced biocompatibility, improved bioavailability, and reduced off-target effects. However, challenges such as reduced bioavailability following systemic delivery and the need for repeated fresh EV isolation hinder their clinical translation. To overcome these limitations, innovative strategies, such as the development of "off-the-shelf" three-dimensional bioprinted hyaluronic acid-based hepatic patches, are being explored[187]. This approach enables the sustained and localized release of encapsulated EVs, potentially in combination with hepatocytes for dual therapy, promoting tissue regeneration. As demonstrated in the MASLD rat model, this bioprinted patch effectively alleviated alterations in biochemical parameters, reduced localized inflammation, and mitigated liver fibrosis. The synergistic effect between the miRNA cargo of released EVs, cell therapy, and bioprinted matrix materials highlights the potential for targeting multiple complex metabolic pathways associated with MASLD. This advancement offers a promising avenue for improving EV-based therapies, addressing current limitations and paving the way for more effective clinical interventions in this challenging liver disease. However, despite compelling preclinical evidence, the translation of EV-based therapies for MASLD into clinical practice remains in its nascent stages. To date, there are no registered clinical trials specifically investigating EV-based interventions for MASLD. This highlights the urgent need for well-designed clinical studies to evaluate the safety and efficacy of EV-based therapies in patients, ultimately paving the way for their integration into clinical management strategies for this prevalent and challenging liver disease.

CHALLENGES AND FUTURE DIRECTIONS

Current challenges in EV research

Standardization of EV isolation and characterization methods: To date, there is no standard method for EV isolation and characterization. This lack of standardization arises from the inherent heterogeneity of the size, composition, and function of EVs. Common isolation techniques, such as ultracentrifugation and size-exclusion chromatography (SEC), present limitations[188]. Ultracentrifugation, while widely used, struggles to fully separate EVs from lipoproteins because of their similar densities and carries the risk of EV rupture, resulting in cargo loss. While SEC is effective for size-based separation, it coisolates EVs with certain lipoproteins, such as very low-density lipoprotein and chylomicrons, leading to sample contamination. Lipoproteins, which are far more abundant in blood plasma than EVs are, further complicate this issue[189]. To mitigate these challenges, researchers have explored optimizing density gradients and combining SEC with other purification methods. Immunoprecipitation against liver-specific EV surface proteins, such as ASGR1, is considered, although it is complex. Ultimately, different isolation methods yield distinct EV subpopulations, impacting downstream analysis, and technological advancements are necessary for efficient, large-scale, and high-purity EV isolation. A better understanding of EV biology is essential for the development of improved isolation techniques.

Similarly, characterizing isolated EVs faces challenges, as the reliability of results is affected by difficulties in isolating EVs from complex biofluids and accurately determining their contents. Techniques such as flow cytometry, resistive pulse sensing, dynamic light scattering, enzyme-linked immunosorbent assay, and nanoparticle tracking analysis are frequently employed for characterization[190]. Surface plasmon resonance approaches have the potential to become the best option for efficient biomarker panel discovery. Surface plasmon resonance holds promise for efficient biomarker panel discovery, and advanced methods such as resistive pulse sensing offer higher size resolution than dynamic light scattering and nanoparticle tracking analysis[191]. While these techniques show clinical relevance, ongoing research aims to improve their sensitivity, specificity, and standardization for broader clinical applications, with future efforts focused on the synergy between label-free EV detection and multiplexed signal analysis to facilitate the clinical translation of EVs

[190,192].

Understanding the complexity of EV cargo and function: The complexity of EV cargo and function stems from their diverse molecular compositions and the intricate mechanisms governing their biogenesis. EVs carry a wide range of biomolecules, including proteins, lipids, and nucleic acids, which play essential roles in intercellular communication and disease progression. However, several challenges hinder their study and application. One major obstacle is the lack of specific marker proteins for EV subtypes, such as exosomes and microvesicles, making it difficult to isolate and purify distinct EV populations effectively[7]. Additionally, EVs exhibit significant heterogeneity in size, composition, and origin, complicating their classification and functional analysis. The mechanisms underlying EV biogenesis, including cargo sorting and release, remain incompletely understood, limiting efforts to manipulate EVs for therapeutic or diagnostic purposes. Furthermore, cargo selection and loading into EVs are influenced by cell type, physiological conditions, and external stimuli, adding another layer of complexity to their study. Addressing these challenges is crucial for advancing the understanding and application of EVs in biomedical research and clinical settings.

Challenges and issues *in vivo* EV tracking: *In vivo* tracking of EVs presents numerous challenges, particularly in the context of complex diseases such as MASLD. The use of exogenously administered EVs from cell lines fails to accurately reflect the natural interplay of endogenous EVs. Some studies have utilized cell lines engineered to express genetic reporters, such as green fluorescent protein or bioluminescence resonance energy transfer-based reporter for extracellular particle fusion proteins, to track EV release from implanted tumors in mice[193]. While fluorescent lipophilic dyes offer a convenient labeling approach, concerns regarding aggregation and signal discrepancy arise[194]. MemGlow™, however, minimizes autofluorescence and is effective in zebrafish models[195]. Tracking EVs secreted directly by specific tissues *in vivo* remains crucial, but the limited applicability of genetically modified cell lines poses a challenge[196]. Researchers have used *ex vivo* blood models to study EV-blood cell interactions, which mimic *in vivo* observations. This approach allows for controlled experiments and studies across multiple species[197,198]. Furthermore, determining the functional activity of specific EV cargoes in recipient cells remains a substantial hurdle, as more robust and consistent methodologies beyond current approaches such as Cre mRNA delivery are needed[199]. Finally, the absence of standardized tracking methods across studies complicates data comparison and impedes the establishment of a cohesive knowledge base.

Addressing translational challenges in clinical applications: EV-based diagnostics for MASLD remain in early developmental stages, with a focus on identifying molecular signatures through omics approaches. Translating these findings into clinically viable tools is a significant challenge. One major limitation is the lack of comprehensive EV databases comparable to genetic repositories, making population-specific data scarce. Additionally, global variations in EV cargo across different ethnic and geographic groups require extensive validation. Another gap lies in the understanding of EV biodistribution and circulation dynamics, as factors such as patient physiology and time of sample collection remain poorly characterized. To advance EV-based diagnostics, large-scale clinical validation is necessary. Despite promising *in vitro* findings, studies on patient-derived samples are crucial to ensure accuracy and applicability across diverse populations before clinical implementation[196]. With respect to EV-based therapies, a more thorough exploration of their pharmacokinetics and biodistribution across various animal models, including nonrodents, is needed. For example, studies using pig-tailed macaques (*Macaca nemestrina*) demonstrated the value of nonhuman primate models for studying human diseases[200].

Single-EV analysis and advanced imaging techniques: Single-EV analysis and advanced imaging have become vital for addressing EV heterogeneity and exploring individual EV variations. These techniques enable the identification of specific EV subpopulations and their unique roles in cell communication[201]. Advanced imaging, such as super-resolution microscopy, allows for the visualization of EV interactions and cargo delivery at the nanoscale, which is crucial for both basic research and clinical applications[202]. By providing detailed insights into individual EVs, these techniques are essential for advancing our understanding of cell-to-cell communication and realizing the full potential of EV-based applications.

Integration of multi-omics data for comprehensive EV profiling: Integrating multiomics data is crucial for advancing EV research because it overcomes the limitations of single-omics analyses, which provide only isolated snapshots of molecular components. While valuable EV databases exist, they lack the capacity to reveal the complex interactions between DNAs, RNAs, proteins, and metabolites that drive biological functions. Combining data from different "omic" layers allows researchers to capture synergistic relationships and the intricate interplay of biological variations, offering a more comprehensive understanding of EV biology in both healthy and diseased states[203]. This integrated approach, whether guided by prior knowledge or driven by data-driven discovery, is essential for uncovering novel biomarkers, therapeutic targets, and a deeper understanding of EV-mediated processes[204].

Potential for personalized medicine

The application of EVs derived from induced pluripotent stem cells (iPSCs) represents a significant advancement in personalized medicine. Given the inherent capacity of iPSCs to be generated from an individual's somatic cells, they offer a platform for autologous therapies, thereby mitigating immunogenic complications[205]. The utilization of iPSC-derived EVs extends this personalized approach by leveraging their cargo for targeted therapeutic intervention[206]. Notably, studies have focused on MSC-EVs and their therapeutic potential in chronic liver diseases, including MASLD. Previous work demonstrated that MSC-EVs obtained from various sources, such as the amnion, adipose tissue, and Wharton's jelly, effectively attenuated HSC and Kupffer cell activation, resulting in reduced inflammation and fibrogenesis[207-209].

Specifically, in murine models of hepatic injury and fibrosis, iPSC-derived EVs exhibited notable therapeutic effects on HSC modulation. Genomic analysis revealed that these iPSC-derived EVs, upon accumulation in the murine liver, were significantly enriched in miR-92a-3p[210]. In essence, the capacity to generate iPSCs from a patient's cells and subsequently derive EVs with specific miRNA cargo enables the development of personalized therapeutic strategies. This approach facilitates the delivery of tailored molecular interventions, thereby increasing therapeutic efficacy and minimizing adverse effects.

CONCLUSION

EVs have emerged as critical mediators of intercellular communication, influencing key processes in MASLD, such as lipotoxicity, inflammation, and fibrogenesis. Their utility as diagnostic and prognostic biomarkers offer a pathway toward minimally invasive and targeted patient care. However, the translation of these promising findings into clinical practice necessitates addressing significant challenges. These include standardizing EV isolation and characterization, unraveling the intricate complexity of EV cargo, and developing robust *in vivo* tracking methods. Future research must prioritize the integration of multiomics data, the refinement of single-EV analysis, and the execution of rigorous clinical trials to overcome translational hurdles. By fostering interdisciplinary collaboration and harnessing cutting-edge technologies, we can pave the way for EV-based precision medicine, ultimately improving patient outcomes in MASLD and other liver diseases.

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